EXHIBIT C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	M. Von Herrath	Art Unit:	1636
Application No.:	09/336,672	Examiner	W. Sandals
Filed:	June 17, 1999		
Title:	COMPOSITIONS AND METHODS FOR THE TREATMENT OR PREVENTION OF AUTOIMMUNE DISORDERS		

#15

Commissioner of Patents
Washington, D.C. 20231

SUPPLEMENTAL DECLARATION OF APPLICANT UNDER 37 C.F.R. §1.132

Sir:

I, Matthias G. von Herrath, M.D., inventor of the above-identified application, do hereby declare and state that:

1. I am familiar with the content of the above-identified application, including the methods for modulating an ongoing immune response to a self-antigen associated with autoimmune diabetes contained in the Specification therein.

2. An experiment in addition to those described in my Declaration under 37 C.F.R. §1.132 signed on December 21, 2000 have been conducted under my supervision and control in the laboratories of The Scripps Research Institute, Department of Neuropharmacology, Division of Biology, in La Jolla, California, using the methods and procedures disclosed in the above-identified application to illustrate the efficacy of the invention methods for modulating an immune response against a self-antigen associated with autoimmune diabetes .

3. In this additional experiment, tests were conducted to determine the effect of induced peripheral expression of self-antigen (porcine insulin B chain) (InsB) on spontaneous occurrence of IDDM in *nod* mice. Mice used in the experiments were female *nod/scid* mice obtained from Jackson Laboratories or *nod* mice bred from *Nod*/LtJ breeders (Taconic Farms) in

which diabetes occurs spontaneously in 80% of the females and 30% of the males by 30 weeks of age.

The mice were vaccinated with a plasmid engineered to express porcine insulin B chain DNA (InsB) under the control of the initial-early promoter of CMV. The plasmid is commercially available, widely used and described previously by Coon et al., *J. Clin. Invest.*, 1999, 104:189; Yokoyama et al., *J. Virol.*, 1995, 69:2684. The IE-CMV promoter has previously been shown to support transcription of various antigens in mammalian cells. The plasmid was expanded and purified from *E. coli*, using the Quiagen method. Alternatively, the mice were administered the InsB-expressing plasmid (pCMV-InsB) together with a plasmid expressing either IL-10 or IL-4 under the control of a HTLV promoter (respectively (pHTLV-IL-10 and pHTLV-IL-4). Immunizations were at the age of 7 days (gluteal muscle) with booster inoculations at 4 and 8 weeks (quadriceps muscle), bilaterally, at a total dose of 100 μg or 50 μg of the pCMV-Ins B + 50 μg of pHTLV-IL-4 or pHTLV-IL-10. in 100 μl of sterile PBS. Controls were naïve mice and mice administered pCMV plasmid without the interleukin The number of mice per group were as follows: naïve, (n=19); pCMV (n=13); pCMV-InsB (n=20), together with a plasmid expressing either IL-10 or IL-4 under the control of a HTLV promoter (respectively (pCMV-InsB + pHTLV-IL-10 (n=9); pCMV-InsB + pHTLV-IL-4 (n=10).

The blood glucose was monitored every two weeks beginning at 10 weeks of age. As shown in Figure 1 attached hereto as Exhibit 1, statistical analysis (p of log-rank test < 0.05) showed a significant suppression of increase in blood glucose levels in nod females immunized with plasmids encoding Ins-B or with a combination of plasmids encoding Ins-B and either IL-4 or IL-10.

Thus, this experiments show that administration to female *nod* mice of a plasmid containing DNA encoding bovine insulin B chain, optionally augmented by administration of a plasmid containing either IL-4 or IL-10, significantly suppressed an increase in blood glucose, a clinical symptom of autoimmune diabetes.

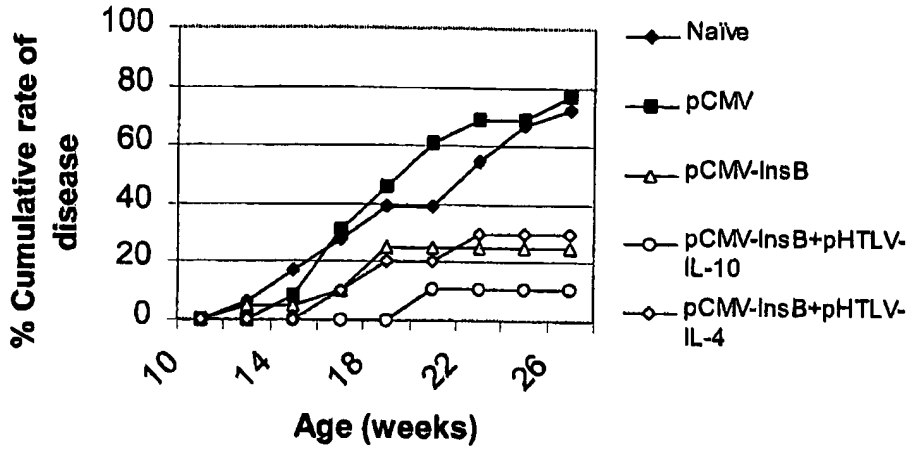
4. I further declare that all statements made herein of knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date

Matthias G. von Herrath, M.D.

Attachments
Figures 1.

Fig. 1. Kinetics of IDDM in *nod* mice immunized with pInsB plasmid



Legend:

Mice were immunized with plasmids (100μg/dose or 50μg + 50μg of plasmid mixture) at the age of 7 days, 4 weeks and 8 weeks. The blood glucose was monitored every other two weeks beginning with 10 weeks of age. Statistical analysis showed a significant suppression of disease in *nod* females immunized with pCMV-InsB, a mixture of pCMV-InsB and pHTLV-IL-10, or pCMV-InsB+pHTLV-IL-4 (p of log-rank test < 0.05). Number of mice / group (naïve, n=19; pCMV, n=13; pCMV-InsB, n= 20; pCMV-InsB+pHTLV-IL-10, n=9; pCMV-InsB+pHTLV-IL-4, n=10).